(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication: 06.11.2002 Bulletin 2002/45

(51) Int CI.7: **A61K 31/702**, A23L 1/30, A23L 1/0528, A61P 27/16

. (11)

(21) Application number: 02015505.7

(22) Date of filing: 02.07.1996

(84) Designated Contracting States:

AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL
PT SE

(30) Priority: 10.07.1995 US 1000 P 12.06.1996 US 653083

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC: 96922652.1 / 0 837 686

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Remarks:

This application was filed on 10 - 07 - 2002 as a divisional application to the application mentioned under INID code 62.

(54) Enteral products containing indigestible oligosaccharides for treating and preventing otitis media in humans

(57) Enteral products containing indigestible oligosaccharides are provided for reducing the incidence of otitis media in infants and young children.

More specifically, the indigestible oligosaccharide is selected from the group consisting of fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides. The indigestible oligosaccharides can be produced through enzymatic synthesis, chemical techniques or isolated from plant materials and are ad-

ministered in the form of a nutritional product, candy, tablets, chewing gums, lozenges, milk products, yogurts and the like.

In a preferred embodiment of this invention, the indigestible oligosaccharides have a DP of 2 to 20 and still more preferably are the fructooligosaccharides GF_2 , GF_3 and GF_4 .

Description

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FIELD OF THE INVENTION

[0001] The present invention relates to a method for reducing the incidence of otitis media by enterally administering to humans an indigestible oligosaccharide. In particular, the present invention relates to a product for enteral administration comprising an indigestible oligosaccharide selected from fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides.

10 BACKGROUND OF THE INVENTION

[0002] Prevention of otitis media in young children is a significant public health problem that has not been solved. Methods of prevention presently available are limited to practices that reduce transmission of infectious agents to susceptible individuals. Such methods include provision of clean water, hand washing, and good personal hygiene. The development of effective vaccines to prevent otitis media has been limited because of the large number of potential pathogens that can cause this disease and because young children, who are at greatest risk, often fail to develop effective immunity. Individuals treated with antibiotics for otitis media and other infectious diseases may become colonized with antibiotic-resistant bacteria and may not respond to antibiotic treatment.

[0003] Fructooligosaccharides (FOS) are natural substances composed primarily of fructose molecules. They belong to a group of carbohydrates that occur in many different plants. FOS are indigestible oligosaccharides that pass through the small intestine without being digested, reaching the large intestine where they are selectively fermented by certain microorganisms. FOS can be utilized efficiently by lactobacilli and bifidobacteria, species of bacteria that are beneficial for human health (Hidaka et al.). Selective fermentation of FOS by bifidobacteria leads to an increase in the presence of these bacteria and to the production of acetic acid and lactic acid as fermentation endproducts, resulting in a lower pH in the digestive tract and providing a means to prevent the overgrowth of harmful bacteria like *Escherichia coli, Clostridium perfringens and Clostridium difficile.* (Hidaka et al., "Fructooligosaccharides: Enzymatic Preparation and Biofunctions", *Journal of Carbohydrate Chemistry* 10(4): 509-522, 1991).

Indigestible Oligosaccharides

[0004] "Indigestible oligosaccharides" refers to a small carbohydrate moiety that is resistant to endogenous digestion in the human upper digestive tract. Fructooligosaccharides (FOS) are indigestible oligosaccharides that are members of the inulin subclass of fructosans, polymers composed of fructose residues. FOS are sometimes characterized by their degree of polymerization. Degree of Polymerization (DP) means the number of covalent bonds between the monosaccharide units in the polymer. For example, the tetramer nystose is composed of three fructose monomers bound to glucose (or sucrose plus two fructose units) and has a DP of 3. Using this nomenclature, sucrose is GF_1 (glucose plus fructose). Specifically, inulins are glucofructosans, carbohydrate polymers consisting of a chain of fructose residues linked by (2-1)- β -glycosidic bonds and usually having a single D-glycosyl residue linked (1-2)- α - to the first fructose molecule.

[0005] Fructooligosaccharides (FOS) can be produced enzymatically, through chemical techniques or by extraction from natural substances. FOS occur in nature in many kinds of plants, including onions, garlic, shallots, artichokes, wheat, rye, bananas, asparagus and tomatoes, that are commonly part of a human diet (Speights et al., "Fructooligosaccharides-A Low Caloric Bulking Agent-And More From Sucrose", *Carbohydrates in Industrial Synthesis*, ed. M. A. Clarke, Proceedings of the Symposium of the Division of Carbohydrate Chemistry of the American Chemical Society, 1992). Another natural source of FOS is the chicory root FOS can also be synthesized from sucrose through the use of transfructosylating enzymes. Treatment of 50% (w/v) sucrose with the transfructosylating enzyme from *Aspergillus niger* results in a mixture of fructooligosaccharides containing 2,3, or 4 fructose residues, designated respectively: 1-kestose or GF₂ in which one molecule of fructose is bound to sucrose; nytrose or GF₃ in which two molecules of fructose are bound to sucrose; and 1^F-β-fructofuranosyl nystose or GF₄ in which three molecules of fructose are bound to sucrose.

[0006] An enzymatic method of producing FOS industrially is disclosed in U.S. Patent No. 4,681,771 to Adachi et al. that comprises reacting sucrose in the presence of a fructosyltransferase (enzyme) to obtain GF_2 , GF_3 , GF_4 , and GF_5 . The source for the enzyme, fructosyltransferase, could be a fungus such as *Aspergillus niger*.

[0007] Richards (U.S. Patent No. 5,318,794) discloses a method for producing a product (caramel) containing between 20 and 50% fructose oligosaccharides, having a degree of polymerization (DP) of about 3-10. The method comprises heating sucrose and an organic acid until fructose oligosaccharides are formed. This method produces a mixture of oligosaccharides, many of which differ in structure from the GF₂, GF₃, and GF₄ used in the present invention. [0008] Richards et al. (WO 94/27618) disclosed a method for the treatment and prevention of diarrhea comprising

administration of a caramel prepared according either to the process of U.S. Patent No. 5,318,794 or according to the process of U.S. Patent No. 5,206,355. WO 94/27618 provides examples of infants and adults suffering from diarrhea who were treated with the caramels. The present invention is, by contrast, directed to the prevention of otitis media in children by prophylactic administration of fructooligosaccharides.

[0009] Analysis of human breast milk has determined that it does not contain the FOS of this invention. Kunz and Rudloff have reported in an article entitled "Biological functions of oligosaccharides in human milk" Acta Paediatr. 82: 903-12 (1993) that the monomers of breast milk oligosaccharides are D-glucose, D-galactose, N-acetylglucosamine, L-fucose and sialic acid. With few exceptions, all of the breast milk oligosaccharides carry lactose at their reducing end. In contrast, the present inventors have discovered that the very different fructooligosaccharides (FOS) with a degree of polymerization of from 2 to 20 can reduce the manifestation of otitis media in a human consuming from 0.5 to 5 grams per day FOS. In a more preferred embodiment, the human consumes 1.0 to 4.0 grams per day and in yet a still more preferred embodiment, the human consumes 1.5 to 3.5 grams per day of FOS.

[0010] Animal toxicology studies have shown no evidence of toxicity, mutagenicity, or carcinogenic effects due to FOS (Clevenger et al., "Toxicological evaluation of neosugar: genotoxicity, carcinogenicity, and chronic toxicity", *Journal of the American College of Toxicology* 7:643-662, 1988). FOS is used in Japan in many food products and has been added to infant formula. (Fructooligosaccharide Information Package, Coors BioTech, Inc. May 1990).

SUMMARY OF THE INVENTION

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[0011] There is disclosed, a method of reducing the incidence of otitis media in a human, said method comprising enterally administering an effective amount of indigestible oligosaccharides to said human. This invention more specifically relates to a method of preventing otitis media in a human, said method comprises enterally administering from 0.5 grams to 5 grams per day of an indigestible oligosaccharide. The indigestible oligosaccharides useful in this invention are selected from fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides. In a preferred embodiment, the fructooligosaccharides are selected from 1-kestose, nystose and 1^F-β-fructofuranosyl nystose. The indigestible oligosaccharides are administered enterally in any convenient form. In one embodiment of the invention, the indigestible oligosaccharides are contained in a nutritional product such as infant formula. Enteral administration of the indigestible oligosaccharides can also be accomplished through their inclusion in products such as infant formula, 'follow-on' formula, toddler's beverages, milk, dietary supplements, fruit juice, fruit based drinks, candies, tablets, chewing gums, lozenges, yogurts and fermented products, or in a liquid. The term "fermented products" means products such as cottage cheese or fermented milk that use specified cultures of microorganisms in their manufacture. It has been found that administration of from 0.5 to 5 grams per day of the indigestible oligosaccharides will be efficacious in reducing the incidence of otitis media in a human.

[0012] In order to demonstrate the present invention a clinical study was undertaken to test whether the enteral administration of FOS would reduce the incidence of otitis media. A controlled 16 week, randomized blinded study was undertaken to determine if feeding indigestible oligosaccharides or fructooligosaccharides would reduce the incidence of otitis media in young children attending day care centers. Children were enrolled in the study and fed one of two study beverages: a milk-based beverage that served as a control or the same milk-based beverage containing FOS (Experimental). The study beverages were the sole source of milk fed to the children during the period of the study. The subjects were placed on active surveillance for illnesses including otitis media upon enrollment into the study. Results of the study show that the incidence of otitis media in subjects consuming FOS was significantly lower than in subjects consuming the control beverage.

DETAILED DESCRIPTION OF THE INVENTION

[0013] As used herein and in the claims "indigestible oligosaccharides" refers to carbohydrates with a degree of polymerization of from 2 to 20 (GF₂ - GF₂₀)and/or a molecular weight less than about 3,600 that is resistant to endogenous digestion in the human upper digestive tract. These "indigestible oligosaccharides" are utilized as a substrate for fermentation by selected bacteria like lactobacilli and bifidobacteria species and other nonpathogenic bacteria that reside in the lower gastrointestinal tract. Indigestible oligosaccharides that may be employed in the preferred embodiments of the invention may be prepared enzymatically, by chemical means or extracted from natural substances. As used herein and in the claims, effective amount of the indigestible oligosaccharide can range from 0.5 - 5 grams per day. [0014] Chemical structures of sucrose and some fructooligosaccharides useful in the practice of the present invention are shown below.

The structure of the general form is shown as GF_n , and the fructosan molecule is designated F_m . Any molecule depicted as GF_n or F_m can be used in the practice of the present invention. These include in the preferred embodiment 1-kestose (GF_2 in which one molecule of fructose is bound to sucrose), nystose (GF_3 in which two molecules of fructose are bound to sucrose), and 1^F - β -fructofuranosyl nystose (GF_4 in which three molecules of fructose are bound to sucrose). In other embodiments of the invention indigestible oligosaccharides such as xylooligosaccharides and galactooligosaccharides will have a degree of polymerization ranging from 2 to 20. Xylooligosaccharides selected from the group consisting of xylobiose, xylotriose and xylotetrose are useful in the present invention. Xylooligosaccharides and galactooligosaccharides [(Galactose)_n-Galactose-Glucose] wherein N can range from 1 to 10 are also useful in the present invention.

[0015] In general, the invention relates to a method of reducing the incidence of otitis media in a human, said method comprising enterally administering a therapeutically effective amount of an indigestible oligosaccharide to said human. The indigestible oligosaccharide is selected from the group consisting of fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides having a degree of polymerization of 2 to 20.

[0016] In a preferred embodiment, the method comprises enterally administering to a human at least 1 gram per day of at least one fructooligosaccharide selected from the group consisting of GF₂, GF₃ and GF₄.

[0017] The present invention also relates to a method of treating otitis media in a human wherein the method comprises enterally administering to the human from 0.5 to 5 grams per day of at least one indigestible oligosaccharide selected from the group of oligosaccharides having a degree of polymerization of from 2 to 20. The indigestible oligosaccharide may be selected from the group consisting of fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides and preferably the fructooligosaccharide is selected from the group consisting of 1-ketose, nystose, and 1^F-β-fructofuranosyl nystose. Preferably, the indigestible oligosaccharide is administered in a nutritional product. The nutritional product may be selected from the group consisting of an infant formula, follow-on formula, toddler's beverage, milk, yogurts, fermented products and dietary supplements. The nutritional product may also be selected from the group consisting of fruit juice and fruit based drinks. Alternatively, the indigestible oligosaccharide is administered in a candy, a chewing gum, a tablet, a lozenge or a liquid.

METHODS AND MATERIALS

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[0018] The indigestible oligosaccharides used in the clinical study were synthesized according to the method disclosed in U.S. 4,681,771 to Adachi et al. The teachings of U.S. 4,681,771 are incorporated herein by reference. The process comprises reacting sucrose in the presence of a fructosyltransferase from *Aspergillus niger* to obtain GF₂,

GF₃, and GF₄. The FOS used in the clinical study was obtained from Golden Technologies, Inc. of Westminster, CO. The Fructooligosaccharides Powder was Lot No. 931115 and had the following chemical analysis:

Moisture -	2.5
Carbohydrate composition (% dry basis)	
Glucose and Fructose -	0.5
Sucrose -	3.5
FOS -	96.0
GF2	41.3
GF3 -	45.7
GF4 -	9.0

[0019] The Fructooligosaccharides Powder was a white powder with a granular size of less than 42 mesh. This FOS was used to prepare the milk-based fortified infant formula substantially in accordance with U.S. Patent 5,021,245, the teachings of which are herein incorporated by reference. More specifically, to produce a 5,700 lb. batch of the powdered Experimental formula, a mixture of 20 lbs. of lactose, 1,100 lbs. of sucrose and 166 lbs. of FOS were dissolved in water. This carbohydrate solution was then combined with the protein, oils and vitamins set forth in Table 1, heat processed, homogenized, spray dried and packaged into containers.

Study Design

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[0020] A controlled, blinded, randomized 16 week study was conducted on children attending day care centers. Children between 10 and 24 months of age were enrolled in the study and fed one of two beverages: a milk-based beverage that served as the control and was designated as Control; the same milk-based beverage that served as the Control formula was supplemented with FOS at 3.5 grams per liter and was designated as Experimental. Milk beverages other than the child's assigned study beverage were restricted. The study beverages were fed *ad libitum* as the sole source of milk.

[0021] At entry into the study, children were placed under active surveillance for otitis media and other significant medical illnesses. Surveillance included study evaluations at days 7, 28, 56, 84 and 112. Research nurses visited the participating day care centers each week to ensure study compliance and identify illness episodes.

Study Diet

[0022] The study beverages were powder products that were reconstituted with water at the point of consumption. The powdered Control and Experimental beverages were reconstituted by mixing 135 grams of powdered nutritional with 1 liter of water. The beverages contained approximately 670 to 725 Kcal per L.

[0023] The powdered products were provided in clinically labeled 400 gram cans. The beverage was a modified, fortified milk-based drink with or without FOS that met the nutrient levels recommended by the Committee on Nutrition of the American Academy of Pediatrics as required by the Infant Formula Act of 1980. The study beverage compositions are shown in Table 1.

[0024] Both beverages provided 20 calories per fluid ounce when reconstituted with water. The average daily intake for children receiving Control beverage was 750 mL and for children receiving Experimental beverage was 766 mL which resulted in consumption of approximately 2.6 grams of FOS per day.

TABLE 1

	IADLE I		
Approximate Co	PRODUCT COMPOSITION imposition of Study Beverage With or Without Fructor	oligosaccharides (per liter)	
NUTRIENT Experimental Study Beverage with Fructooligosaccharides Experimental Study Beverage with Fructooligosaccharides			
Protein, g	15.3	15.3	
Fat,g	37.2	37.2	
Carbohydrate, g	74.7	74.7	
Linolenic Acid, mg.	6500	6500	
Vitamin A, IU	2900	2900	

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TABLE 1 (continued)

NUTRIENT	Experimental Study Beverage with	Control Study Beverage
•	Fructooligosaccharides	·;
Vitamin D, IU	440	440
Vitamin K, mcg	112	112
Thiamine (B ₁), mcg	239	239
Riboflavin (B ₂), mcg	1505	1505
Vitamin B ₁₂ , mcg	3.24	3.24
Niacin, mcg	9000	9000
Folic Acid (Folacin), mcg	155	155
Pantothenic Acid, mcg	. 4250	4250
Biotin, mcg	45.0	45.0
Vitamin C (Ascorbic Acid), mg	150	150
Choline, mg	ຸ 156	156
Inositol, mg	38	38
Calcium, mg	975	′ 975
Phosphorus, mg	650	650
Magnesium, mg	75	75
Iron, mg	13	13
Zinc, mg	8.5	8.5
Manganese, mcg	52	52
Copper, mcg	710	710
Sodium, mg	220	220
lodine, mcg	46	46
Potassium, mg	840	840
Chloride, mg	620	62 0 .
Taurine, mg	57.5	57.5
Energy (Kcal)	684	684
β-Carotene, mcg	400	400
% Kcal from protein	8.95	8.95
Nucleotides, mg	72	72
FOS	3.5	0

Study Subjects and Entry Procedures

[0025] Children were randomly assigned to receive Experimental or Control. The children were in apparent good health with no history of aspiration pneumonia, chronic gastroenteritis or diarrhea within seven days prior to enrollment. Subjects were prohibited from receiving human milk feedings for the duration of the study and had a history of ingesting whole cow's milk or cow's milk-based formula.

[0026] Day care center records and clinic or physician visits were monitored for clinically significant illnesses, such as diarrhea, bronchitis, bronchiolitis, and otitis media. Research nurses and physicians reviewed day care center records and clinic or physician records to document illnesses.

Statistical Methods

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[0027] The number of children with otitis media and the number of episodes of otitis media in each feeding group were analyzed by the Cox regression analysis, using the marginal approach to multivariate survival analysis. The analysis of the number of episodes of otitis media counts all episodes including repeated episodes.

Incidence of Otitis Media

[0028] The incidence of otitis media in subjects consuming the experimental beverage containing FOS was significantly lower than in subjects consuming the Control beverage. Fifty subjects had documented episodes of otitis media during the course of the study: 17 of the 131 subjects receiving the Experimental beverage and 32 of the 134 subjects receiving Control. This is statistically significant with a probability of p = 0.023. Results are summarized in Table 2.

Table 2

		1
OTITIS ME	EDIA EPISODES	
	EXPERIMENTAL BEVERAGE	CONTROL BEVERAGE
	N=131	N=134
NUMBER OF CHILDREN HAVING OTITIS MEDIA*	17	33
REPEAT EPISODES OF HAVING OTITIS MEDIA	9	18
TOTAL NUMBER OF EPISODES OF OTITIS MEDIA**	26	51

^{*}p = 0.023 by Cox Regression Analysis

[0029] It is concluded from the results of the clinical study that administration of an indigestible oligosaccharide such as FOS reduces the incidence of otitis media in children. The reduced incidence of otitis media seen in the group of children fed FOS was unexpected. The prior art does not suggest or disclose that enteral administration of FOS would be effective in preventing the incidence of otitis media.

[0030] According to the present invention, it has been discovered that sugars selected from the indigestible oligosaccharides, particularly fructooligosaccharides can prevent the occurrence of otitis media.

[0031] The present invention provides a method for reducing the incidence of otitis media. Indigestible oligosaccharides can be added to various nutritional products including but not limited to infant formula and products for older children and adults, such as 'follow-on' formulas and toddler's beverages and also milk and yogurt products. They can be formulated in candies, tablets, lozenges, chewing gums and also mixed into dietary supplements and other liquid and powdered foods.

Industrial Applicability

[0032] The occurrence of otitis media is a major healthcare problem. The medical community has few tools to prevent and treat this disease, therefore the present invention will fulfill a long felt need. It is surprising that the enteral administration of naturally occurring indigestible oligosaccharides or sugars would be effective in reducing otitis media in humans.

[0033] While various embodiments of the present invention have been described in detail, it will be apparent to those skilled in the art that modifications and adaptations will occur to those skilled in the art. However, it is to be expressly understood that such modifications and adaptations are within the scope of the present invention, as set forth in the following claims.

Claims

- 1. A product for enteral administration comprising an indigestible oligosaccharide selected from fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides.
- 2. The product of Claim 1 wherein said indigestible oligosaccharide has a degree of polymerization of 2 to 20.
- 3. The product of Claim 1 wherein said oligosaccharide is selected from 1-kestose, nystose and 1^F-β-fructofuranosyl nystose.
- 4. The product of Claim 1 wherein said indigestible oligosaccharide consists of a mixture of 1-kestose, nystose and 1^F-β-fructofuranosyl nystose.

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[&]quot;p = 0.0486 by Multivariant Cox Regression Analysis

- 5. The product of any one of Claims 1-4 wherein said indigestible oligosaccharides are included in products selected from infant formula, follow-on formula, toddler's beverage, milk, dietary supplements, fruit juice, fruit-based drinks, candy, chewing gum, tablets, lozenges, yogurts and fermented products.
- 6. The product of any one of Claims 1-4 wherein said product is a nutritional product.

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- 7. The nutritional product of Claim 6 wherein said indigestible oligosaccharides are included in products selected from infant formula, follow-on formula, toddler's beverage, milk, yogurts, fermented products and dietary supplements.
- 8. The nutritional product of Claim 6 wherein said indigestible oligosaccharides are included in products selected from fruit juice and fruit-based drinks.
- 9. The product of Claim 3 wherein said indigestible oligosaccharides are included in products selected from yogurts and fermented products.
 - 10. The nutritional product of Claim 6 wherein said indigestible oligosaccharides are included in an infant formula.
- 11. The product of any one of Claims 1-4 wherein said indigestible oligosaccharides are included in products selected 20 from candy, chewing gum, tablets and lozenges.

(11) **EP 1 254 664 A3**

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3: 02.01.2004 Bulletin 2004/01

(51) Int CI.7: **A61K 31/702**, A23L 1/30, A23L 1/0528, A61P 27/16

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- (71) Applicant: Abbott Laboratories
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 - Hilty, Milo Duane Lewis Center, OH 43035 (US)
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More specifically, the indigestible oligosaccharide is selected from the group consisting of fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides. The indigestible oligosaccharides can be produced through enzymatic synthesis, chemical techniques or isolated from plant materials and are ad-

ministered in the form of a nutritional product, candy, tablets, chewing gums, lozenges, milk products, yogurts and the like.

In a preferred embodiment of this invention, the indigestible oligosaccharides have a DP of 2 to 20 and still more preferably are the fructooligosaccharides GF_2 , GF_3 and GF_4 .



Application Number

which under Rule 45 of the European Patent Convention EP 02 01 5505 shall be considered, for the purposes of subsequent proceedings, as the European search report

	DOCUMENTS CONSIDE	RED TO BE RELEVANT	·	
Category	Citation of document with inc of relevant passag		Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.7)
Х	WO 92 08368 A (WRIG 29 May 1992 (1992-09 * claims 1-4,6,7 *	LEY W M JUN CO) 5-29)	1-11	A61K31/702 A23L1/30 A23L1/0528 A61P27/16
X	of fructooligosacche human colonic bacter ABSTRACTS OF THE GEI AMERICAN SOCIETY FO	ria" NERAL MEETING OF THE R, 4, page 255 XP008023761 g of the American ology;Las Vegas,	1,2,5-11	·
х	WO 94 22327 A (RAFF; FRIPPIAT ANNE (BE) 13 October 1994 (1994 examples 1-4 * claims 1-9 *	94-10-13)	1,2,5-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
	MPLETE SEARCH	-/		A61K A23L A61P
not compl be carried Claims se Claims se Claims no		pplication, or one or more of its claims, does/o meaningful search into the state of the an car , for these claims.		
	sheet C			
	Place of search	Date of completion of the search		Examiner
	THE HAGUE	30 October 2003	van	der Kooij, M
X : part Y : part	ATEGORY OF CITED DOCUMENTS icularly relevant if taken alone icularly relevant if combined with anoth rment of the same category	L : document cited for	ument, but publis the application rother reasons	
A tech	nnological background I-written disclosure	& : member of the sar		



INCOMPLETE SEARCH SHEET C

Application Number

EP 02 01 5505

Claim(s) searched completely: 3, 4 and 9

Claim(s) searched incompletely: 1, 2, 5-8 and 10-11

Reason for the limitation of the search:

Present claims 1-2, 5-8 and 10-11 relate to a large number of undefined compounds terms of an indigestible oligosaccharide selected from fructooligosaccharides, fructosans, xylooligosaccharides and galactooligosaccharides" (claims 1, 5-8 and 10-11) or "indigestible oligosaccharides with a degree of polymerization of 2 to 20" (claims 2, 5-8 and 10-11). In fact, the claims contain so many options, that a lack of clarity and conciseness within the meaning of Article 84 EPC arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely relating to products comprising of 1-kestose, nystose or 1F-beta-fructofuranosyl nystose and mixtures thereof (claims 3 and 4).



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EP 02 01 5505

	DOCUMENTS CONSIDERED TO BE RELEVANT	CLASSIFICATION OF THE APPLICATION (Int.CI.7)	
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
χ	EP 0 529 414 A (YAKULT HONSHA KK) 3 March 1993 (1993-03-03) * page 3, line 23 - line 30 * * examples 1,2 * * claim 1 *	1,2,5-11	
X	CHONAN O ET AL: "Effect of galactooligosaccharides on calcium absorption and preventing bone loss in ovariectomized rats." BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY. JAPAN FEB 1995, vol. 59, no. 2, February 1995 (1995-02), pages 236-239, XP008023787 ISSN: 0916-8451 * page 236, column 2, paragraph 2 * table 2 *	1,2,5-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	GB 2 105 338 A (MEIJI SEIKA KAISHA) 23 March 1983 (1983-03-23) * page 3, line 22 - line 34 * * tables 1,2 * * examples 1-3 *	1-11.	
X	US 4 927 811 A (QUARLES CAREY L) 22 May 1990 (1990-05-22) * column 4, line 16 - line 67 * * column 6, line 14 - line 28 * * example 1 * * claims 1-6 *	1-11	
	-/		
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	DOCUMENTS CONSIDERED TO BE RELEVANT	CLASSIFICATION OF THE APPLICATION (Int.CI.7)	
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X,D	WO 94 27618 A (UNIV MONTANA) 8 December 1994 (1994-12-08) * page 7, line 21 - page 8, line 13 * * page 8, line 27 - line 30 * * page 10, line 3 - line 10 * * page 10, line 11 - line 17 * * page 11, line 24 - line 31 * * page 11, line 32 - page 12, line 1 * * page 13, line 29 - line 35 * * examples 1-3 * * claims 1-3,6,8-13 *	1-11	
Х	EP 0 474 046 A (HOKUREN) 11 March 1992 (1992-03-11) * page 2, line 6 - line 8 * * page 4, line 35 - line 36 * * claims 1-4,10,13 *	1-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
х	US 5 032 579 A (SPEIGHTS ROBERT M ET AL) 16 July 1991 (1991-07-16) * column 10, line 22 - line 32 * * claims 21-23,27-29 *	1-11	
X	US 4 902 674 A (SPEIGHTS ROBERT M) 20 February 1990 (1990-02-20) * column 2, line 44 - line 52 * * column 3, line 8 - line 13 * * column 4, line 22 - line 67 * * claims 9-12,14-19 *	1-11	
	-/		



Application Number

EP 02 01 5505

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	DOCUMENTS CONSIDERED TO BE RELEVANT	Bolessent	APPLICATION (Int.CI.7)
ategory	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
x	WILLIAMS C H ET AL: "Influence of dietary neosugar on selected bacterial groups of the human faecal microbiota" MICROBIAL ECOLOGY IN HEALTH AND DISEASE, vol. 7, no. 2, 1994, pages 91-97, XP008023765 ISSN: 0891-060X * page 91, column 2, paragraph 1 * page 92, column 1, paragraph 3 *	1-11	
X	IKEDA T ET AL: "Low-cariogenicity of the tetrasaccharide nystose." GENERAL PHARMACOLOGY. ENGLAND 1990, vol. 21, no. 2, 1990, pages 175-179, XP000617609 ISSN: 0306-3623 * page 176, column 2, paragraph 2 *	1-11	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	CLEVENGER M A ET AL: "TOXICOLOGICAL EVALUATION OF NEOSUGAR GENOTOXICITY CARCINOGENICITY AND CHRONIC TOXICITY" JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY, vol. 7, no. 5, 1988, pages 643-662, XP000614148 ISSN: 0730-0913 * page 643, paragraph 2 * * page 644; figure 1 * * page 646, paragraph 4 *	1-11	
P,X	EP 0 710 447 A (MEIJI SEIKA KAISHA) 8 May 1996 (1996-05-08) * page 3, line 13 - line 18 * * claim 6 *	1-11	

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 02 01 5505

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

30-10-2003

WO	9208368	A					
		^	29-05-1992	WO	9208368	A1 .	29-05-199
			•	ΑU	666884	B2	29-02-199
				AU	2870292		03-05-199
				CA		Ä1	31-03-199
				ĒΡ	0607326		27-07-199
				ĴΡ	2641323		13-08-199
				ĴΡ	7502644		23-03-199
				WO	9306740		15-04-199
				US	5425961		20-06-199
WO.	9422327	A	13-10-1994	BE	1006893	A3	17-01-199
,,,		• •	20 20 200	ĀΤ		7	15-05-199
				ΑÜ	687792		05-03-199
				AU	6255994		24-10-199
				WO	9422327		13-10-199
				CA	2159316		13-10-199
				DE	69410060		10-06-199
			•	DE	69410060	T2	12-11-199
				DK	651614	T3	01-02-199
				EP	0651614	A1	10-05-199
				ES	2116588	T3	16-07-199
	•			US	6521276	B1	18-02-200
EP	0529414	Α	03-03-1993	JР	2571734	B2	16-01-199
				JP	5049397	Α	02-03-199
				ΑU	649857	B2	02-06-199
				ΑU	2063392		25-02-199
				CA	2075157	A1	24-02-199
				DE	69206077	D1	21-12-199
				DE	69206077	T2	18-07 - 199
				EP		A1	03-03-199
				KR	184526		20-03-199
				US	5466472	Α	14-11-199
GB	2105338	A	23-03-1983	JР	58040065		08-03-198
				DE	3232531	A1	17-03-198
US	4927811	A	22-05-1990	CA	2002712	A1	15-05-199
wo	9427618	Α	08-12-1994	US	5439893	Α	08-08-199
				AU	6946594		20-12-199
				WO	9427618	A1	08-12-199
EP	0474046	Α	11-03-1992	JР	4235192	Α	24-08-199
				JР	6070075		07-09-199
				DE	69117231	D1	28-03-199

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 02 01 5505

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely, given for the purpose of information.

30-10-2003

	Patent documer cited in search rep		Publication date		Patent family member(s)	Publication date
ΕP	0474046	Α		EP US	0474046 A1 5463038 A	11-03-1992 31-10-1995
US	5032579	Α	16-07-1991	US US AT AU CA DE DE EP WO AU EP WO	4902674 A 4987124 A 122888 T 2625588 A 1337045 C 3853888 D1 3853888 T2 0381700 A1 3501971 T 8903218 A1 6728690 A 0500688 A1 9107181 A1	20-02-1990 22-01-1991 15-06-1995 02-05-1989 19-09-1995 29-06-1995 02-11-1995 16-08-1990 09-05-1991 20-04-1989 13-06-1991 02-09-1992 30-05-1991
US	4902674	A	20-02-1990	AT AU CA DE DE EP JP WO US	122888 T 2625588 A 1337045 C 3853888 D1 3853888 T2 0381700 A1 3501971 T 8903218 A1 4987124 A 5032579 A	15-06-1995 02-05-1989 19-09-1995 29-06-1995 02-11-1995 16-08-1990 09-05-1991 20-04-1989 22-01-1991
EP	0710447	A	08-05-1996	JP JP AT CA DE DE DK DK EP ES ES FR GB IT PT US	3155889 B2 8023889 A 206874 T 2153850 A1 19525537 A1 69523253 D1 69523253 T2 81595 A 710447 T3 0710447 A2 2088373 A1 2165885 T3 2722953 A1 2291777 A ,B RM950480 A1 710447 T 5714181 A	16-04-2001 30-01-1996 15-11-2001 14-01-1996 18-01-1996 22-11-2001 11-07-2002 14-01-1996 26-11-2001 08-05-1996 01-08-1996 01-04-2002 02-02-1996 07-02-1996 15-01-1996 28-02-2002 03-02-1998

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82